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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Compans *et al.* : Group Art Unit: 1617

Serial No. 09/803,649 : Examiner: M. Bahar

Filed: March 9, 2001 : Confirmation No. 6596

For: TRANSCUTANEOUS IMMUNIZATION
FOR LARGE PARTICULATE ANTIGENS

APPELLANT'S BRIEF UNDER 37 C.F.R. 1.192

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I. Real Party in Interest

In the present application, the inventors, Richard W. Compans and Zhiyi Sha have assigned their rights in this invention to Emory University. The assignment has been recorded in the Patent and Trademark Office at Reel 013220, Frame 0586.

II. Related Appeals and Interferences

There are no other appeals or any interferences pending in this application.

III. Status of Claims

Claims 1-2, 5, 7-18, and 21-23 are currently pending in this application with the entry of the Amendment submitted herewith. Claims 17 and 22- 23 are as-filed claims, claims 3-4, 6, and 19-20 have been canceled without prejudice, and claims 1, 2, 5, 7-16, 18, and 21 have been amended in the Amendment submitted herewith.

Claims 1-2, 5, 7-18, and 21-23 have been rejected and are under appeal.

IV. Status of Amendment

The Amendment filed on August 8, 2003 in response to the Final Office Action has not been entered. An Amendment which simplifies the issues for appeal is submitted herewith.

V. Summary of the Invention

The present invention provides noninvasive methods for inducing an immune response in a human or animal. Specifically, a particulate antigen of 50-200 nm in diameter is administered without the aid of cholera toxin or cholera toxoid protein onto the unbroken skin of a human or animal in whom the immune response is desired. Such

transcutaneous administration of a particulate antigen results in at least a humoral response specific to at least one component of the particulate antigen. The particulate antigen can be a virus particle, a virus-like particle, a mycoplasma cell, a bacterial cell, membranous preparation, and desirably where the particle is a virus or a cell, the preparation has been treated to inactivate any ability to replicate or to result in an otherwise harmful effect on the human or animal. Virus or virus-like particles can include, but are not limited to, orthomyxoviruses and paramyxoviruses and others, including influenza virus, parainfluenza virus, a hepatitis virus, measles virus, vaccinia virus, herpes virus, rhinovirus. Desirably, the virus particle has a sialic acid binding moiety on its surface. Viruses which have a sialic acid binding surface component include the orthomyxoviruses and the parainfluenza viruses. Influenza virus is an important specific example. In addition, mixed virus particles can be engineered to display a heterologous sialic acid binding component on their surfaces, for example, a hemagglutinin derived in terms of coding sequence from influenza virus. In the case of such engineered virus particles, the particles can also contain antigenic determinants of viruses including other enveloped viruses (including noninfectious HIV, SIV, FIV and others) and those viruses with glycoproteins having terminal sialic acid residues. Additional virus examples are vesicular stomatitis virus, rabies virus, measles virus, flavivirus, and alphaviruses and herpes viruses.

VI. The Issues

Whether claims 1-2, 5, 7-18, and 21-23 are unpatentable under 35 U.S.C. § 103(a) as obvious over Glenn *et al.* (US Patent No. 5,980,898).

VII. Grouping of the Claims

Claims 1-2, 5, 7-18, and 21-23 have been rejected under 35 U.S.C. § 103(a) as allegedly obvious over Glenn *et al.*

The claims pending in this application stand or fall together in this appeal.

VIII. Arguments

A. The claims are not obvious over Glenn *et al.* (U.S. Patent No. 5,980,898).

1. The Rejection and the Claims Affected.

Claims 1-2, 5, 7-18, and 21-23 have been rejected under 35 U.S.C. § 103(a) as allegedly obvious over Glenn *et al.*

The Examiner states:

Glenn *et al.* (U.S Patent No. 5,980,898) teaches a transcutaneous immunization formulation comprising antigen and an adjuvant to unbroken skin and without perforation of the skin induces an immune response, see abstract particularly. Glenn *et al.* further teaches that the antigen may be derived from a virus, see col. 3, lines 64-65. Among the viruses that can be used in the practice of the invention Glenn teaches hepatitis, influenza, measles and vaccinia, see particularly col. 9, line 13-24.

Glenn *et al.* (U.S. Patent No. 5,980,898) does not teach the method of inactivating the viruses, neither does it teach the size of the antigenic particles in nm.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to inactivate the viruses by

any of the widely known methods in the art. As to the particle size, note that the claimed particle size must include non-intact virus.

One of ordinary skill in the art would have been motivated to employ any of the viruses taught in Glenn *et al.* in a transcutaneous immunization formulation because they are known to be useful in transcutaneous formulation used to induce an immune response. Furthermore the different methods of inactivating viruses is within the purview of the skilled artisan.

2. The Patent Office has not made out a *prima facie* case of obviousness because there is no motivation provided in the cited art for practicing the claimed invention.

To make a *prima facie* case of obviousness, the Patent Office must cite a reference that suggests the claimed invention as a whole. Northern Telecom, Inc. v. Datapoint Corp., 15 U.S.P.Q.2d 1321, 1323 (Fed. Cir. 1990) ("It is insufficient that the prior art disclosed the components of the patented [invention], either separately or used in other combinations; there must be some teaching, suggestion, or incentive to make the combination made by the inventor.") In re Oetiker, 24 U.S.P.Q.2d 1443 (Fed. Cir. 1992) ("[t]here must be some reason, suggestion, or motivation found in the prior art whereby a person of ordinary skill in the field of the invention would make the combination" and "[t]hat knowledge can not come from the applicant's invention"); and In re Dow Chemical Co., 5 U.S.P.Q.2d 1529, 1531 (Fed. Cir. 1988) ("The consistent criterion for determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have a reasonable likelihood of success, viewed in light of the prior art.....Both the

suggestion and the expectation of success must be found in the prior art, not in the applicant's disclosure.")

Appellants respectfully submit that the cited reference does not provide the requisite motivation to modify the prior art method to recreate the claimed invention as amended with the entry of the Amendment presented herewith.

Appellants respectfully argue that the cited reference does not suggest the claimed method for inducing an immune response using a composition containing particulate antigens of 50-200 nm in diameter which does not also contain cholera toxin or toxoid. Glenn *et al.* teaches a method of immunization using **soluble** proteins that are derived from various pathogens including viruses. Furthermore, the method of Glenn *et al.* requires the use of an adjuvant such as cholera toxin. This is evident in the examples provided in Glenn *et al.* There is no teaching or suggestion in Glenn *et al.* to motivate a person of ordinary skill in the art to make the invention as claimed, i.e., a method for inducing an immune response by administering onto the unbroken skin a composition containing the particulate antigens of about 50-200 nm in diameter without the aid of cholera toxin or cholera toxoid.

The allegation in the Office Action that Glenn *et al.* teaches that the antigen may be derived from a virus is based on the statement, "The antigen may be **derived from** a pathogen that can infect the organism (e.g., bacterium, virus..." (column 3, lines 64-65).

Applicants submit that the quoted statement was made in the context to indicate that an antigen is a molecule, part of a pathogenic organism such as virus (e.g., viral coat protein) for use in the Glenn *et al*'s method. This is evident in view of the examples described in the cited patent. Nothing in the quoted statement would have taught or motivated a person of ordinary skill in the art that

the particulate antigens of 50-200 nm in diameter (virus or virus-like particle) without cholera toxin or cholera toxoid can be used to induce an immune response when administered onto the unbroken skin, as efficiently as demonstrated in the present application.

The allegation that "among the viruses that can be used in the practice of the invention, Glenn teaches hepatitis, influenza, measles and vaccinia." is based on the statement, "Viruses include, for example: adenovirus, ...hepatitis ....influenza, measles and vaccinia..." (column 9, lines 13-24).

Applicants point out that the above statement was made in Glenn *et al.* in the context to provide a list of infectious pathogens against which the antigens (i.e., soluble proteins) can be used for vaccination, not as the antigens, as taught in the present application. This is evident in the two preceding paragraphs, from column 8, line 66 to column 9, line 12.

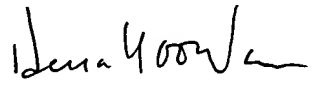
The present invention is a method for inducing an immune response using a particulate antigen (e.g., a virus or a virus-like particle) of 50-200 nm in diameter without the aid of cholera toxin or cholera toxoid protein, which is administered through the unbroken skin. The inventors were the first to discover this method. When this discovery was made, it was not expected in the art that relatively large particulate antigens (without an adjuvant) would induce an efficient immune response when administered onto the unbroken skin, as demonstrated in the present application. The claimed invention is not taught or suggested by Glenn *et al.*, particularly the quoted passages in the Office Action. Glenn *et al.,* at best, provides mere speculation without presenting any actual data. The Examiner is yet to identify specifically the principle, known to one of ordinary skill, which suggests the claimed invention based on the cited reference. See *In re* Lee 61, U.S.P.Q.2d, 1430 (Fed. Cir. 2002).

Based on the foregoing arguments, Appellants respectfully urge that none of the claims are *prima facie* obvious over the cited reference. The present invention meets a long-felt need in the art for a simple and efficient method of transcutaneous immunization.

IX. Conclusion

Appellants have met all the statutory requirements for patenting their invention. They are therefore entitled to patent protection. It is respectfully requested that the outstanding rejection be overruled and the application passed to issuance.

Respectfully submitted,



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APPENDIX A

CLAIMS UNDER APPEAL

1. A method for inducing an immune response comprising the step of applying to the unbroken surface of the skin a composition comprising a particulate antigen and a pharmaceutically acceptable carrier, wherein said particulate antigen is of diameter from about 50 to 200 nm and said composition does not comprise cholera toxin or cholera toxoid protein.

2. The method of claim1 wherein the particulate antigen is an inactivated virus particle.

5. The method of claim 2 wherein the particulate antigen is about 100 nm in diameter.

7. The method of claim 2 wherein the inactivated virus particle is selected from the group consisting of an orthomyxovirus particle and a paramyxovirus particle.

8. The method of claim 7 wherein the inactivated virus particle is an influenza virus particle.

9. The method of claim 1 wherein the particulate antigen is a virus-like particle.

10. The method of claim 9 wherein the virus-like particle comprises hemagglutinin.

11. The method of claim 10 wherein the hemagglutinin is incorporated into the particle by mixed infection with an orthomyxovirus or a paramyxovirus.

12. The method of claim 2 wherein the particulate antigen comprises mixed inactivated virus particle comprising hemagglutinin which is heterologous to the virus.

13. The method of claim 12 wherein the hemagglutinin is a recombinant hemagglutinin of influenza virus or parainfluenza virus.

14. The method of claim 12 where the hemagglutinin is incorporated through mixed infection with an orthomyxovirus or a paramyxovirus.

15. The method of claim 12 wherein the virus particle is a noninfectious particle of parainfluenza virus, hepatitis C virus, hepatitis B virus, measles virus, vaccinia virus, herpes virus or respiratory syncytium virus.

16. The method of claim 2 wherein the virus particle has been inactivated by chemical treatment, ultraviolet irradiation, heat treatment or psoralen treatment.

17. The method of claim 16 wherein the chemical treatment is formalin treatment.

18. A method for inducing an immune response comprising the step of applying to the unbroken surface of the skin a composition comprising a particulate antigen of diameter from about 50 to 200 nm and a pharmaceutically acceptable carrier, wherein said particulate antigen is an attenuated virus particle and said composition does not contain cholera toxin or cholera toxoid protein.

21. The method of claim 18 wherein the attenuated virus particle contains hemagglutinin.

22. The method of claim 21 wherein the hemagglutinin is derived from an orthomyxovirus or a paramyxovirus.

23. The method of claim 22 wherein the hemagglutinin is derived from influenza virus or a parainfluenza virus.